June 9, 2005

Lester M. Crawford, D.V.M, Ph.D
Acting Commissioner of Food and Drugs
US Food and Drug Administration
U.S. Department of Health and Human Services
Parklawn Building
5600 Fishers Lane, Room 1547
Rockville, MD 20857

Dear Dr. Crawford:

I am writing to request more information regarding the FDA's expedited approval process for class III medical devices.

As you know, a class III device is a "novel high risk medical device for which there is a requirement to demonstrate reasonable assurance of safety and effectiveness."[1] However, in an effort to get important health care technologies to the public quickly, the Center for Devices and Radiological Health (CDRH) has an expedited approval process for class III medical devices that is similar to the accelerated approval process for drugs and biologics. At the time of a Premarket Approval (PMA), there may be unanswered questions about the safety and/or effectiveness of the medical device. Under these circumstances, CDRH may require the manufacturer to conduct a "Condition of Approval" (CoA) study. This allows the company to market the device while collecting further information on the device's safety and effectiveness. Like the accelerated approval process, if a device company fails to comply with the conditions of approval, the approval can be withdrawn.

The Center for Devices and Radiological Health (CDRH) released a report, examining the expedited approval process for class III medical devices. According to the report, released on March 18, 2005, a review was initiated "in 2002, because of a growing concern that CoA studies were not being performed or completed by some manufacturers as required…" The internal report concluded that the system is broken.

According to the FDA report,

> Our study suggests that performance of Condition of Approval Studies is suboptimal, with no available study results for many PMAs years after they have been approved, failure of the manufacturer to start or perform the study, potentially fraudulent data from one (1) study, and status of 'study unknown' to

[1] http://www.fda.gov/oc/whitepapers/epi_rep.pdf

> the reviewer (4)… The study also revealed that due to a lack of Center systems for tracking Condition of Approval Studies, it is very difficult for anyone to obtain information on the studies or their status, unless that person has extensive knowledge of the individual products under study…We requested information on 45 PMAs for the three year period. Overall, we received files for 19/45 (42%) PMAs from POS/PAS staff... Staff was unable to retrieve any information for the majority of PMAs (58%). Based on the information found in the annual reports, staff located interim or final study results for 15/45 (33%) of PMAs. In addition, staff forwarded some evidence that a study was underway, but no data was yet available (a study protocol or mention in the annual report that the study was underway), for an additional 3/45(6.7%) of PMAs.[2]

Despite the fact that the CDRH is concerned about lack of company compliance with the process, CDRH has never enforced compliance by withdrawing a device's approval. According to the report, "The Approval Order Letter to the manufacturer explicitly states that failure to comply with the Conditions of Approval invalidates the approval. However, this circumstance has not been used to revoke a PMA."

The report also noted some other very serious problems with company compliance. According to the report, the manufacturer of Adcon-L adhesion barrier gel submitted potentially fraudulent data to the FDA.[3] According to the report, the data is being re-reviewed. The product has been on the market for 7 years.

The report also indicated that the "Manufacturer will not do study" required for the Eclipse TMR Holmium Laser System. It is unclear from the report why the manufacturer will not do the study. Additionally, there are several products without final results that the lead reviewer [for the product] identified as "due."

These findings are very disturbing and appear to mirror the concerns raised in my recent report on the Center for Drug Evaluation and Research (CDER)'s accelerated approval process. However, the two Centers' responses to suggestions of problems with the two expedited review systems differed dramatically.

The Center for Devices and Radiological Health noted that many of the reviewers at the CDRH were very concerned about the effectiveness of the condition of approval process. The report cites concerns such as, "inadequate compliance by manufacturers with CoA studies; lack of FDA authority to obtain compliance; lack of continuity between reviewers including turnover and shifting responsibilities due to changes in branch and division make-up; lack of agency action for poor performance, undermining incentive for manufacturers to perform studies appropriately or in a timely manner." Clearly CDRH is concerned about the effectiveness of the process.

However, when I raised concerns about the accelerated approval process for drugs and biologics, the FDA suggested that there were not any concerns about the effectiveness of the accelerated approval process or their ability to ensure company compliance. The FDA responded that,

[2] http://www.fda.gov/oc/whitepapers/epi_rep.pdf
[3] http://www.fda.gov/oc/whitepapers/epi_rep.pdf

"Assuring completion of these studies in a timely manner is part of [CDER's] routine responsibilities as is prompt and careful review of the studies as they are planned and submitted…To date, there have not been any withdrawals of products approved under accelerated approval related to a failure of the sponsor to conduct the required post-marketing confirmatory trial… When warranted there have been public discussions of delays in conversion of applications… to full approval."[4]

The contrast between the Centers' reactions to suggestions of a problem with their respective expedited systems is stark. Although the problems with the condition of approval process and the accelerated approval process appear to be very similar in nature, CDRH recognizes the problems and appears willing to resolve the issues, while CDER does not appear to acknowledge the existence of any problems.

I applaud the Center for Devices and Radiological Health for conducting this report and for their willingness to make improvements in this process. I believe that it is the FDA's responsibility to enforce completion of all required post-marketing confirmatory studies and condition of approval studies.

I am planning on introducing legislation to address this situation and I would like some more information regarding the FDA's efforts in this area. In this regard, I request your assistance in providing answers to the following questions:

1. According to the report, reviewers at CDRH are concerned about "inadequate compliance by manufacturers with CoA studies." However, the report does not identify the companies that have made these commitments. Please identify the companies that are associated with the condition of approval studies listed in the appendices.
2. Of the products with outstanding studies to ensure safety and effectiveness, how many of the products are still being used by consumers? Please identify these products.
3. Of the products with outstanding studies to ensure safety and effectiveness, are there any studies that the FDA believes are no longer necessary to ensure safety and effectiveness? If so, please identify the studies that are no longer necessary and explain how the FDA reached that conclusion. Has the FDA notified the companies that the studies are no longer necessary?
4. What action has been taken with regard to the manufacturer that submitted potentially fraudulent data to the FDA with regard to the product Adcon-L adhesion barrier gel? When did the FDA first raise questions about the authenticity of the data? What is the penalty for submitting fraudulent data? What enforcement mechanisms does the FDA have to ensure that companies submit data that is complete and accurate?
5. The report also indicated that the "Manufacturer will not do study" required for the Eclipse TMR Holmium Laser System. Why will the manufacturer not do the study? Has the manufacturer refused to do the study? Does the FDA believe that the study is still necessary? If so, what actions is the FDA taking to ensure that the study is completed.
6. According to the report, there are several products without final results that the lead reviewer [for the product] identified as "due." What does the FDA do to let companies

[4] FDA letter to Rep. Markey dated March 30, 2005.

know that their studies are due? What actions is the FDA taking to ensure that the studies are completed on a timely basis?

7. According to the report, "Staff was unable to retrieve any information for the majority of PMAs (58%)." What is the FDA doing to collect complete information on these studies and determine the status of these studies?
8. According to the report, reviewers at CDRH are concerned about "lack of FDA authority to obtain compliance." What further authority would be helpful in ensuring compliance with condition of approval commitments?
9. According to the report, reviewers at CDRH are concerned about "lack of continuity between reviewers including turnover and shifting responsibilities due to changes in branch and division make-up." What is the agency doing to address this concern?
10. According to the report, reviewers at CDRH are concerned about "lack of agency action for poor performance." How does the agency take action for poor performance? Please cite specific examples of actions taken to ensure adequate performance.
11. According to the report, reviewers at CDRH are concerned about "undermining incentive for manufacturers to perform studies appropriately or in a timely manner." What does the agency do to ensure that the manufacturers perform studies appropriately or in a timely manner?
12. Do these concerns (about inadequate compliance by manufacturers, lack of FDA authority to obtain compliance, lack of continuity between reviewers including turnover and shifting responsibilities due to changes in branch and division make-up lack of agency action for poor performance, undermining incentive for manufacturers to perform studies appropriately or in a timely manner) also apply to CDER's accelerated approval process? If so, which concerns are the same? If not, please explain why they do not apply.
13. Has the Center for Drug Evaluation and Research ever undertaken an internal review similar to the Center for Devices and Radiological Health review? If not, why?
14. According to the report, "Interviews with POS/PAS indicated that there was no formal mechanism to track progress of CoA studies. Nor was there any formal mechanism for ascertaining whether the lead reviewer had received, reviewed, or acted on any results from a CoA study." The report provides a number of recommendations to address these issues. Please identify which recommendations have already been implemented and the dates that they were implemented and provide a timeline for implementation of the other recommendations.
    - "Responsibility for tracking and monitoring CoA Studies should be transferred to the Office of Surveillance and Biometrics, which has the responsibility for postmarket patient safety studies.
    - Formal standards and procedures for tracking all Condition of Approval Studies should be introduced. Tracking should include dates due, annual or other reports
    - Condition of Approval Studies as a Postmarket Tool 10 from manufacturers that include study results or evidence that study is underway, and any regulatory actions that are taken because of results from Condition of Approval studies (or lack of results).
    - Annual Reports or other reports with evidence of progress or results from Condition of Approval Studies should be indexed in IMAGE to make them easy to retrieve.

- Due dates for Condition of Approval Studies should be concrete and enforced by closely tracking the status of the reports and reviewing the Center's enforcement options.
- Manufacturers should be queried and reminded when Condition of Approval study results are not provided on schedule.
- Since Condition of Approval studies are often proposed by the FDA's advisory panels when reviewing PMA applications, feedback should be given to the responsible panel on a routine basis regarding the progress and results of these studies.
- Study requirements and periodic status reports for Condition of Approval Studies should be posted on the Agency's website along with similar status reports from CDER and CBER.
- Establish a procedure for taking action when commitments to perform Condition of Approval Studies are not met. Consideration should be given to applying/adopting the provisions we promulgated to enforce §522 (Postmarket surveillance studies) to CoA studies when sponsors fail to fulfill the conditions in the PMA letter."[5]

15. Please identify any other steps that the FDA has taken to ensure that companies complete condition of approval studies on a timely basis.
16. Has there been any communication between the Center for Devices and Radiological Health and the Center for Drug Evaluation and Research about the similarities and differences between the two expedited approval systems and ways to improve them? If so, when and what was the result? If not, why?

Thank you for your assistance and cooperation in this matter. Should you have any questions about this request, please contact Ms. Katharine Reinhalter or Mr. Jeffrey Duncan of my staff at 202-225-2836.

Sincerely,

Edward J. Markey
Member of Congress

[5] http://www.fda.gov/oc/whitepapers/epi_rep.pdf